Distinguishing neuromyelitis optica spectrum disorder from multiple sclerosis using magnetic resonance imaging techniques

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Citation: UBCMJ. 2017: 9.1 (13-15)

Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is a rare neuroinflammatory central nervous system disorder, characterized by astrocytopathy with secondary demyelination. NMOSD and multiple sclerosis (MS) have overlapping clinical manifestations, making NMOSD clinically challenging to distinguish. A highly specific serum antibody test is available that can distinguish NMOSD from MS, but it is not very sensitive to NMOSD. The similarity of NMOSD clinical and imaging features to those of MS, and the lack of awareness about NMOSD among physicians could lead to misdiagnosis. Distinguishing NMOSD from MS is important as prognosis and treatment options differ. Here, we will discuss myelin water imaging, an advanced quantitative magnetic resonance imaging technique to explore the pathology of lesional and normal–appearing tissues of MS and NMOSD. We will also review machine learning methods that automatically distinguish between the two diseases. Both techniques are actively being studied at the University of British Columbia.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare central nervous system disorder that typically presents with optic neuritis, longitudinally extensive transverse myelitis, and area postrema clinical syndrome.[1] It is characterized by an antibody–mediated attack on water channels expressed on astrocytes and in the ensuing inflammatory response, secondary demyelination occurs.[1] Due to similar clinical manifestations, NMOSD was thought to be a subtype of multiple sclerosis (MS), which is an autoimmune disorder of the brain and spinal cord characterized by edema, inflammation, demyelination and axonal damage, resulting in impaired saltatory conduction.[2] Examples of these overlapping clinical symptoms include vision loss, weakness in extremities, fatigue and sensory dysfunction. However, NMOSD has emerged as a distinct disorder from MS since the discovery of serum aquaporin 4 immunoglobulin G antibodies (AQP4–IgG) in 2004.[3,4] This autoantibody marker is very specific (97-99%) to NMOSD; however, it is not as sensitive (59-76%).[4] This means that some patients who test seronegative for AQP4–IgG may still have NMOSD. Therefore, other imaging biomarkers or differentiation techniques are highly desirable to classify NMOSD from MS. The similar clinical and imaging features of NMOSD and MS, and the lack of awareness about NMOSD among physicians could lead to misdiagnosis, especially if the patient is AQP4–IgG seronegative with the presence of brain lesions. Differentiating NMOSD from MS has crucial implications to prognosis and treatment because standard MS therapy, such as interferon-beta, may worsen NMOSD and increase relapses.[5]

To better understand the different pathology of NMOSD and MS, magnetic resonance techniques can be used. Magnetic resonance imaging (MRI) is a non–invasive medical imaging tool that utilizes a strong magnetic field to align or anti–align magnetic moments of protons (termed spins), mainly from water, and use radio frequency pulses to manipulate the spins, generate signal, and produce images with high spatial resolution.[6] Conventional MRI is frequently used in diagnosis and clinical management of NMOSD and MS. It is useful for visualizing lesion distributions in space and time. However, the limitations of this imaging modality include low specificity to pathological processes, low sensitivity to diffuse damage in the normal-appearing white matter, and limited association with clinical status in both MS and NMOSD.[7] Therefore, there is significant ongoing research into using advanced MRI techniques to better understand pathological processes such as demyelination and axonal loss in disease–specific tissues. Here, we discuss myelin water imaging, which can be used to investigate the differences in pathological processes in both lesional and normal–appearing tissues of NMOSD and MS, as well as machine learning approaches that are used to automatically distinguish between NMOSD and MS for early and accurate diagnosis of NMOSD. Both techniques are currently actively studied at the University of British Columbia.[8-13]

Myelin Water Imaging

Myelin is a fatty substance that envelops the axon and enables saltatory conduction, allowing increased conduction velocity.[14] Damage to myelin slows the transmission of information sent along the axon and causes the exposed axon to degenerate. Therefore, a measurement of myelin content *in vivo* can be useful in better understanding demyelinating diseases such as MS and NMOSD.

Myelin water imaging (MWI) is an advanced, quantitative MRI technique that was developed and pioneered by Dr. Alex MacKay's group at the University of British Columbia in 1994.[15] MWI uses multi–echo T2 relaxation measurements to quantify the fraction of signals originating from three major water compartments in healthy human brain: a long T2 (~2 sec) from cerebrospinal fluid, an intermediate T2 (~60-80 msec) from intra– and extracellular water, and a short T2 (~15-20 msec) from water trapped between the myelin bilayers.[6,15,16] The myelin water fraction (MWF) is defined as the ratio of water between myelin bilayers to the total water content.[6] Furthermore, the MWF has been validated as a marker for myelin content by histopathological analysis using a myelin–specific stain in postmortem human brain tissues.[17] Since its validation, many studies have focused on MWF to better understand MS and NMOSD pathology.

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In 2016, Jeong et al. compared the MWF in periventricular white matter lesions in 27 relapsing–remitting MS and 20 AQP4 IgG-positive NMOSD patients, as periventricular white matter is commonly affected in both conditions.[18] They found that the mean MWF in MS periventricular lesions (4.06±2.69%) was significantly lower than in NMOSD periventricular lesions (6.18±3.15%) (p=0.002).[18] Furthermore, they found that 59.4% of the MS lesions, compared to 33.3% of the NMOSD lesions, had severe (≥75%) myelin loss (p=0.001), thereby suggesting that there is more severe demyelination in MS than in NMOSD.[18] However, Jia et al.[19] noted that the data must be interpreted with caution, as MWF was reported to vary among different lesion types in MS.[20]

Additionally, Matthews et al. found several normal-appearing white matter regions with significant MWF reduction in the MS cohort over one year; however, this change was not seen in NMOSD or controls.[21] Therefore, there were widespread neurodegenerative changes in MS but not NMOSD cohorts, which may support the clinical finding of progression in MS but little or no progression in NMOSD.[21]

In contrast to studies done by Jeong et al. and Matthews et al., a combined transcranial magnetic stimulation (TMS) and MWI study showed lower TMS recruitment curve slopes and lower MWF in the corticospinal tract in NMOSD, compared to MS and controls. This suggested greater damage in NMOSD than in MS.[13] The conflicting results may be due to small sample size and different patient population, particularly since the disease course of MS is very heterogeneous.

Currently, there is active research focusing on myelin water imaging at the University of British Columbia. For example, Combes et al. investigated potential diffuse myelin changes in NMOSD by computing z-score MWF maps from a MWF atlas that was created from healthy control data.[8] This illuminated how much MWF in NMOSD deviated from the normal.[8] They found that the volume of abnormal MWF in MS (378±542 voxels, p=0.001) and NMOSD (126±205 voxels, p=0.1) were higher than in healthy controls (33±65 voxels).[8] Furthermore, lesion volume was significantly correlated with volume of abnormal MWF (p=0.02) and average normal–appearing white matter z-score (p=0.009) in MS; however, this pattern was not detected in NMOSD.[8] In the future, further longitudinal studies with larger datasets investigating the difference in MWF in brain and spinal cord lesions and normal–appearing white matter are warranted.

Finally, even though MWF has been shown to correlate with histological stains of myelin,[17] there are some confounding factors that may affect *in vivo* measurement of MWF. For example, after myelin damage in MS and NMOSD, macrophages clear myelin debris from the injury site. If the myelin debris is not cleared efficiently, it may affect MWF. Animal studies have shown that myelin debris may affect MWF;[22-24] however, this has not been studied in human tissues.

Machine Learning Approach

Machine learning-based pattern recognition techniques have advantages over human observation, such as their ability to take a large number of variables into consideration and improve classification with consistency.[25-32] Additionally, this predictive approach of using machine learning can help to better differentiate NMOSD and MS in a way that it is reproducible and interpretable. Recently, this technique has gained much popularity in psychiatric disorders[26,27] and neurodegenerative disorders such as Alzheimer's disease,[25,28] traumatic brain injury,[29] and clinically isolated syndromes.[30]

In 2015, Eshaghi et al. used a machine learning algorithm on support vector machines, and found that the average accuracy to differentiate NMOSD and MS was 88% using both conventional and advanced imaging techniques.[31] Here, white matter lesion load, normal–appearing white matter integrity, and functional connectivity were the most important factors for distinguishing between NMOSD and MS.[31] A limitation of this study was that it was conducted at a single centre, thereby failing to ensure generalizability of its model to a global patient population.

Therefore, in 2016, Eshaghi et al. used a random–forest, which is another machine learning algorithm for classification, from two sites, using only conventional imaging techniques.[32] They found that the cortical thickness, volume, and surface area measures resulted in average accuracy, sensitivity and specificity of 74%, 77% (i.e., 77% of true MS cases were classified as MS), and 72% (i.e., 72% of true NMOSD cases, without MS, were correctly classified), respectively, to distinguish between MS and NMOSD.[32] When they combined thalamic volume, the most discriminating gray matter measure, with white matter lesion volume, it resulted in higher average accuracy, sensitivity, and specificity of 80%, 85% and 76%, respectively between NMOSD and MS, in two sites.[32] Given these results, a machine learning approach that automatically differentiates NMOSD from MS would be advantageous as the main method for differentiating between the two diseases. In comparison, the AQP4-IgG serum test method is highly specific (97-99%) but not as sensitive (59-76%).[4]

Currently, researchers from the University of British Columbia are developing a machine learning algorithm to distinguish NMOSD from MS as well.[9] The aim is to use a machine learning approach based on artificial neural networks, called deep learning, to determine if the patterns of brain MRI lesions and measures derived from diffusion tensor imaging (DTI) can automatically discriminate between NMOSD and MS.[9] DTI is a quantitative MRI technique that measures characteristics of water diffusion and it is influenced by—but not specific to—myelin content, axonal damage, inflammation or edema.[6] Preliminary results on 82 NMOSD and 52 MS patients have shown that deep learning can achieve an accuracy rate of 81%, thereby demonstrating the potential of deep learning to distinguish NMOSD from MS using patterns of brain lesions and diffusion tensor imaging metrics.[9] A limitation of the machine learning method is that it is not a hypothesis–driven approach. Instead, it reveals relationships upon receiving large amounts of information, but it cannot guarantee these are causal relationships. In the future, the machine learning approach can be further studied to differentiate NMOSD with and without AQP4-IgG.

Conclusion

Although conventional imaging is useful in the diagnosis and clinical management of neuroinflammatory diseases such as NMOSD and MS, it faces limitations including low specificity to pathological processes, and limited association with clinical status in MS and NMOSD. Quantitative MR measures can provide valuable information on pathology and can be used to develop machine learning algorithms to facilitate earlier and more accurate diagnosis of NMOSD automatically. Myelin water imaging can successfully detect the differences in myelin content between lesional and normal–appearing NMOSD and MS tissues. Therefore, MWI can provide insight on disease progression and treatment efficacy. Furthermore, machine learning–based pattern recognition techniques using gray matter measures alone or in combination with white matter lesion load, as well as DTI metrics, have

the potential to distinguish NMOSD from MS automatically. All these techniques may facilitate earlier and accurate differential diagnosis in clinical practice.

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